At p. 43, line 12, delete "uL" and replace with - -μL- -.

At p. 43, line 16, delete "Tween 20" and replace with - -TWEEN 20 detergent- -.

At p. 43, line 19, delete "nile red" and replace with - -NILE RED dye- -.

At p. 43, line 20, delete "um" and replace with - -μm- -.

At p. 44, line 1, delete "by wt" and replace with - -(w/w)- -.

At p. 44, line 3, delete "nile red" and replace with - -NILE RED dye- -.

At p. 44, line 5, delete "Nile Red" and replace with - -NILE RED dye- -.

At p. 44, line 7, delete "Tween 20" and replace with - -TWEEN 20 detergent- -.

At p. 45, line 5, delete "11" and replace with - -11A and 11B- -.

At p. 45, line 10, delete "12" and replace with - -12A and 12B- -.

In the Claims

32. (Amended) The method of claim 28 wherein said [sensor array] elements comprise[s a population of] beads [dispersed on a substrate].

REMARKS

Claims 28-38 are pending and finally rejected. Claim 32 is amended to recite that the elements comprise beads. Support is found throughout the specification, for example at p. 28, lines 3-6. Applicants respectfully request entry of the amendments. Applicants submit that no new matter is added in the amendment. For the Examiner's convenience a copy of the pending claims is appended hereto.

Response to Amendment of February 11, 2000

Applicants appreciate the Examiner's entry of those amendments that were entered. As to the amendments to page 41, lines 3-7 and 12-21 and pages 42-25 that were not entered, Applicants appreciate the telephonic interview with the Examiner on June 8, 2000 that clarified the nature of the amendment defects. Applicants have attempted herein to submit an amendment

that overcomes the defects of the prior amendment. Applicants respectfully request entry of these amendments.

Information Disclosure Statement

Applicants appreciate the Examiner supplying the publication months of the references submitted in the citation of January 6, 2000 and December 2, 1999. With respect to the Drmanac et al articles submitted in the citation of January 6, 2000, Applicants submit that the year of publication is sufficiently earlier than the effective U.S. filing date of the present application so that the particular month of publication is not an issue (MPEP § 609). That is, the articles were published in 1990, 1992 and 1994, while the present application was filed October 6, 1997.

The Examiner indicates that the information disclosure statement (IDS) filed December 2, 1999 fails to comply with 37 CFR 1.98 (a)(2) which requires a legible copy of each U.S. and foreign patent. It is noted that the information disclosure statement has been placed in the application file, but the information referred to has not been considered.

In response, Applicants respectfully submit that the references were supplied with the information disclosure statement. In support of this Applicants are submitting herein a copy of the Information Disclosure Statement mailed November 26, 1999 that states that "[c]opies of the references are enclosed" (see p. 1 of the Information Disclosure Statement). Furthermore, Applicants are submitting herein a copy of the postcard that indicates that 65 references were submitted. Accordingly, Applicants submit that the requirements of 37 CFR 1.98(a) have been met by Applicants. However, for the Examiner's convenience, submitted herein are copies of the references and a copy of the IDS mailed November 26, 1999. Applicants respectfully request consideration of the references.

Response to Rejections

Response to Rejection Under 35 U.S.C. § 103

Claims 28-38 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. patent no. 5,866,331 (Singer et al.). Singer is directed to a method of single molecule detection in *in situ* hybridization of an individual probe bound to a target molecule. The total flourescence intensity (TFI) per fluorochrome is determined; this can be used to determine the number of

probes bound, which is a determination of the presence of the target molecule. In determining the TFI, Singer sums the individual pixels within an optical section of a single probe in solution. The probe solution is placed between and in contact with the microscope slide and a cover slip (see col. 2, lines 25-27), and the signal produced within a defined optical section is determined. The volume of the imaged section is then determined. Based on the known concentration of the probe, the summed signal and the total volume imaged, the TFI is determined.

Basically, the Office Action emphasizes that it would have been obvious to one of ordinary skill in the art, to take the method of determining TFI as disclosed in Singer, to form the method of increasing the signal-to-noise ratio as presently claimed. That is, the Office Action relies on the disclosure of Singer that describes summing pixels of an image of a fluorescent probe solution and asserts that this renders obvious the presently claimed invention. Applicants respectfully traverse.

Initially Applicants would like to draw the Examiners attention to terms that the Examiner seems to use interchangeably. However, Applicants submit that the terms are distinct. Namely, in the Final Rejection the Examiner notes that Singer teaches a "sensor array having subpopulations of different sensor elements (probes which are different based at least on their spatial location)". In this regard it appears that the Examiner is referring to the teaching in Singer of localizing labeled probes at different locations within a cell, for example as demonstrated in Figure 2 of Singer. The Examiner then appears to assert that Singer teaches summing "at least two of the sensor elements". The Examiner points to col. 7, lines 1-2 as support for summing. However, Applicants respectfully note that column 7, lines 1-2 are describing summing pixels obtained from an image of a probe in solution, not a signal obtained from probes localized at different locations within a cell.

The purpose of the invention of Singer is to quantify the Total Fluorescence Intensity of a probe (i.e. determine the fluorescence/mol of probe) so that the number of copies of a target can be determined. Thus, although Singer describes summing pixels to obtain the Total Fluorescence Intensity of a probe solution, it does not teach summing the optical response of the probes when immobilized to their targets.

In contrast to the Singer reference, Applicants note that the present claims are directed to a method of increasing the signal-to-noise ratio in the optical response of a sensor array. The

array has subpopulations of different sensor elements. The method further includes measuring the optical response signature of at least two of the sensor elements and summing the optical response signatures.

Applicants respectfully note that a valid rejection under 35 U.S.C. §103 based upon a single prior art reference must be supported by some suggestion of the claimed invention or motivation to reach the claimed invention which is found in that single prior art reference. In re Laskowski, 10 USPQ2d 1397 (CAFC 1989). In addition, all of the claim elements must be found in the prior art.

To this end, Applicants note that there is no teaching or suggestion in Singer of a method as presently claimed, wherein at least two sensor elements of a subpopulation are measured and summed. Applicants respectfully note that the pixels of Singer, which the Examiner appears to equate to the sensor elements of the presently claimed invention, are derived from an image of a single probe in solution. They are not themselves sensor elements. Accordingly, Singer fails to provide a suggestion of the claimed invention.

Moreover, Applicants submit that there is no teaching in Singer that would motivate one of ordinary skill in the art to reach the claimed invention. That is, upon reading Singer, the skilled artisan would not be motivated to measure the optical response signature of at least two sensor elements of a population and sum the optical responses.

Moreover, Applicants submit that even if there was motivation to reach the claimed invention, the teachings of Singer fail to provide a reasonable expectation of success in practicing the claimed invention. First, as described above, the pixels of Singer are not equivalent to the sensor elements of the present claims. However, Singer fails to disclose summing anything other than pixels. Furthermore, with respect to dependent claim 32, Applicants submit the beads on the microscope slide and coverslip as taught in Singer, are not sensor elements as presently claimed. That is, although it is noted that Singer teaches that "[w]hen suspended in aqueous solution, such beads randomly settle onto glass surfaces" (col. 8, lines 60-62), Applicants submit that beads as described in Singer are not sensor elements. Rather, beads serve as "first and second fluorescent point sources" (col. 8, line 54)). The purpose of the beads in this context is to attach to the microscope slide and the cover slip and serve as references so that the distance (the z axis distance (col. 8, line 30) between the slide and cover slip can be determined. However,

claim 32 recites that the sensor elements comprise beads.

With respect to dependent claim 33, the Examiner indicates that the selection of a fiber optic bundle as a substrate in place of a microscope slide or cover slip would have been within the ordinary skill in the art. However, Applicants note that the method as disclosed in Singer requires both the cover slip and microscope slide. That is, as described at col. 8, lines 15-21 "the imaged volume **10** is the three-dimensional portion of the sample **12** from which fluorescent light is collected.... The z axis is perpendicular to the microscope slide and the coverslip." Thus, Singer requires a determination of the imaged volume. This necessarily requires a determination of the image viewed in the X and Y plane, but also the Z axis. Accordingly, without both the coverslip and microscope slide, there would be no way to determine the volume that was imaged.

In light of the requirement of both the slide and the cover slip, Applicants respectfully submit that substitution of a fiber optic bundle for the slide and coverslip would not have been obvious to the skilled artisan. Furthermore, Applicants submit that such a substitution would destroy the function of the slide and the coverslip. That is, substituting a fiber optic bundle for the slide or coverslip of Singer would preclude the determination of the imaged volume, thereby rendering the teaching of Singer inoperative. The Examiner's attention is respectfully drawn to MPEP 2143.01 that notes that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

Accordingly, Applicants submit that the disclosure of Singer actually teaches away from using a substrate such as a fiber optic bundle. To this end, Applicants note that in Dow Chemical Co. v. American Cyanamid Co., 2 USPQ2d 1350 (CAFC 1987), the Federal Circuit affirmed a district court holding that various patents were not invalid as obvious over a prior art reference because the prior art reference "taught away" from the inventions in those patents.

With respect to dependent claim 34, the Examiner looks to the abstract, line 6 as support for the teaching in Singer of identifying the location of each sensor element within each sensor subpopulation within the array. Lines 6-7 of the abstract recite that the method "has sufficient resolution and sensitivity to locate and detect a single target-bound probe". Applicants submit that this statement does not support the requirement of the identification of each sensor element of a subpopulation of elements on an array. Rather, this is a statement of the sensitivity of the

method of Singer.

With respect to dependent claim 35, the Examiner notes that the sensor elements of Singer comprise chemical functional groups. However, Applicants submit that in this regard, the Examiner appears to be referring to a modified oligonucleotide as a sensor element as opposed to the pixel as described above. Applicants note that the Examiner appears to be picking and choosing within the Singer reference those definitions that support a particular rejection. However, Applicants respectfully submit that such inconsistency is improper. The Examiner is respectfully directed to Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 230 USPQ 416 (Fed. Cir. 1986) where the Federal Circuit held that a single line in a prior art reference should not be taken out of context and relied upon to show obviousness under 35 U.S.C. § 103. Rather, the Federal Circuit held that a prior art reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered.

Likewise, the Examiner's assertion that the sensor element of Singer comprises an oligonucleotide (as in dependent claim 36) appears to be an inconsistent analogy of the term "sensor element" as claimed.

As to Claims 37 and 38, Applicants submit that Singer fails to disclose a method of amplifying the characteristic optical response of a sensor array wherein the array has subpopulations of different sensor elements.

CONCLUSION

Singer fails to provide the motivation for reaching the claimed invention. Furthermore, Singer files to provide a reasonable expectation of practicing the claimed invention. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection should be withdrawn.

Applicants submit that the claims are now in condition for allowance and an early notification of such is solicited. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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Dated: September 14, 2000
1020637

Pending claims:

28. A method for increasing the signal-to-noise ratio in the characteristic optical response signature of a sensor array having subpopulations of different sensor elements comprising:

a) measuring the optical response signature of at least two of said sensor elements of at least one of said subpopulations; and

b) summing the optical response signatures.

29. A method according to claim 28 wherein prior to said summing, the baseline of at least one optical response signature is adjusted.

30. A method according to claim 28 wherein the signal-to-noise ratio is increased by a factor of at least 10.

31. The method of claim 28 wherein an analyte detection limit is reduced by a factor of at least 100.

32. (Amended) The method of claim 28 wherein said [sensor array] <u>elements</u> comprise[s a population of] beads [dispersed on a substrate].

33. The method of claim 32 wherein said substrate is a fiber optic bundle.

34. The method of claim 32 further comprising identifying the location of each sensor element within each sensor subpopulation within the array.

35. The method according to claim 28 wherein said sensor elements comprise chemical functional groups.

36. The method according to claim 28 wherein said sensor elements comprise oligonucleotides.

37. A method for amplifying the characteristic optical response signature of a sensor array having subpopulations of different sensor elements comprising:

a) measuring the optical response signature of at least two of said sensor elements of at least one of said subpopulations; and

b) summing the optical response signatures.

38. A method according to claim 37 wherein prior to said summing, the baseline of at least one optical response signature is adjusted.